REMARKS

Claims 1-71 are in this application. Claims 3, 9, 18-51, 53, 56-62 and 64-68 are withdrawn. Claim 7 was amended to delete the second occurrence of the word "analgesics." Claim 52 was amended to define a method for treating a health disorder, disease or medical condition comprising administering a composition according to claim 7 to a patient in need thereof wherein the health disorder, disease or medical condition can be treated by the biologically active agent of claim 7. New claims 69-71 are being added. Claim 69 defines a method for treating a health disorder, disease or medical condition comprising administering a composition according to claim 8 to a patient in need thereof wherein the health disorder, disease or medical condition can be treated by the biologically active agent of claim 8. Claims 70 and 71 define a method for preventing a health disorder, disease or medical condition comprising administering a composition according to claim 7 or 8, respectively to a patient in need thereof wherein the health disorder, disease or medical condition can be prevented by the biologically active agent of claim 7 or 8 respectively.

Applicants again respectfully traverse the restriction requirement and maintain that the claims of groups I, II and III should be examined in this application. The Examiner has referred the applicants to US Patent 6,632,457 (Sawhney et al.) and states that this reference teaches that surfactants such as Tween and Span are soluble in the water phase. Tweens are known to be water-soluble and play no role in the formation of the gelled dispersion. The Spans on the other hand play a key role as they gel the continuous oil phase of the invention. All Spans are known to be water-insoluble (see attached references, Handbook of pharmaceutical Excipients and European Pharmacopoeia – monographs about sorbitan esters and sorbitan stearate) and are incapable of gelling either the oil phase or the polymer-solution phase as required by the instant application. Thus, the use of water as a vehicle instead of oil will not allow the formation of the product as described in the instant application. Also, in claim 1 of this application the emulsifiers are sorbitan monostearate, sorbitan monopalmitate or a mixture thereof. These are the only emulsifiers known to gel the oils and the solvents of

the invention. Therefore, applicants submit that the claims of groups I, II and III should be examined in this application.

In view of the amendment of claim 7, the objection to claim 7 is moot.

The Examiner has rejected claim 52 under 35 USC 112, first paragraph as not being enabled. Applicants respectfully traverse this rejection.

Claim 52 has been amended and new claims 69-71 have been added which define that the method of treatment or method of prevention is obtained using a composition of claim 1 wherein the biologically active agent is one of either claim 7 or claim 8. These claims also define that the health disorder, disease or medical condition is one that can be treated or prevented by the biologically active agent of claim 7 or 8. One skilled in the art would understand that health disorders, diseases or other medical conditions can be treated and/or prevented by administration of a composition of claim 1 which includes a biologically active agent of claim 7 or 8. One of ordinary skill in the art knows that the biologically active agents defined in claims 7 and 8 can be used to treat and/or prevent health disorders, diseases or other medical conditions. It is known that antineoplastics and antitumor compounds can be used to treat and in some cases, prevent a recurrence of certain types of cancer (i.e. tamoxifen). Antiallergenics can be used to treat allergies or administered prophylactically can prevent the allergic reaction. In the case of prevention, a gelled dispersion of the invention could be used to deliver, for example, vaccines over a period time which is definitely a preventive measure. Another example of preventing a health disorder, disease or medical condition is the administration of an antimalarial drug which can be used to prevent malaria. A still further example is the administration of antibiotics which can be used to prevent health disorder, disease or medical conditions that result from infections caused by biological agents such a bacteria, etc.

Therefore, it is clear that claim 52 and claims 69-71 are enabled. It is respectfully requested that this rejection be withdrawn.

The Examiner has rejected claim 7 as being indefinite under 35 USC 112, second paragraph. Applicants respectfully traverse this rejection.

The Examiner questions the phrase genetic material because it is not clear how said material differs from the DNA fragments and nucleic acids recited in the claims. Genetic material includes RNA and RNA fragments. One skilled in the art would know this because of skill in the art would know of the existence, for example, of RNA viruses such as orthomyxoviruses, picornaviruses, togaviruses, coronavirus, ebola virus, paramyxoviruses, etc.

Therefore, it is respectfully requested that this rejection be withdrawn.

The Examiner has rejected claims 1, 2, 5-8, 11-17, 52, 54, 55 and 63 under 35 USC 103(a) as being unpatentable over Sawhney (US Patent 6,632,457). Applicants respectfully traverse this rejection.

The two compositions, the one described by Sawhney in the above cited patent and the instant application are different and have completely different mechanisms for the delivery of biologically active agents. The Sawhney patent discloses hydrogel matrices made from macromers. The matrices are comprised of "a continuous hydrogel matrix, wherein the hydrogel matrix is formed by chemical reaction of macromers; a hydrophobic phase dispersed within the hydrogel matrix; and a therapeutic agent dispersed within the hydrophobic phase, the hydrophobic phase controlling a rate of release of the therapeutic agent from the hydrogel matrix" – See for example claim 1 and col. 8, lines 1-15 of Sawhney. The compositions are prepared by dissolving or dispersing the therapeutic agent in the hydrophobic domain either as a solution to form a microdroplet, with or without a release rate modifying agent, which hydrophobic domains are then uniformly distributed within an aqueous solution of macromers which is further polymerized to form the hydrogel matrix.

A comparative description highlighting the differences between the respective compositions is provided below :

No.	Sawhney (U.S. 6,632,457)	Bhagwatwar et al. (US 2003/0049320 A1)
1.	The continuous phase is a polymeric hydrogel. The continuous phase here does not contain any oil.	The continuous phase is a gel obtained from the gelling of an oil by the gelling action of sorbitan monostearate, sorbitan monopalmitate or a mixture thereof. Also, the continuous phase is non-polymeric
2.	The discontinuous phase or hydrophobic domain is comprised either of preformed particles through the use of waxes, fatty acids or fatty alcohols or through the use of an oil with an added release rate modifier. Both could contain a biologically active agent. These form the microdroplets described in this patent.	The discontinuous phase is comprised of a biodegradable / non-biodegradable polymer dissolved in a biocompatible water-soluble organic solvent. The biologically active agent of claim 7 or 8 is dissolved, dispersed or suspended therein. The microdroplets used here are thus completely different from those described in the Sawhney patent.
3.	The discontinuous phase could comprise preformed microparticles.	Preformed microparticles are not used.
4.	The discontinuous phase releases the biologically active agent rapidly upon coming in contact with the aqueous fluids; column 12, lines 6-8.	The discontinuous phase can release the drug in a continuous controlled fashion over a prolonged period of time upon coming in contact with the aqueous fluids.
5.	The composition as described in this application upon coming in contact with aqueous fluids swells because of	The composition as described in this application upon coming in contact with aqueous fluids does not swell as

	the hydrogel nature of the continuous phase and the biologically active agent is released through the diffusion of fluids through the water-swollen pores of the hydrogel to the microdomains and then out again to the fluids. A diffusion gradient is thus set up and the release rate is also dependent upon the size of the pores, among other parameters.	the continuous phase is extremely lipophilic. A primary mechanism of drug release is by the formation of polymeric microcarriers through the contact of the polymer-solvent droplets with the aqueous medium and the subsequent biodegradation of the polymer. A secondary mechanism of drug release is by its dissolution into the oily continuous phase and then by further partitioning into the aqueous medium.
6.	The term "in situ" as used in this application is meant to describe the formation of the hydrophobic phase during the formation of the hydrogel phase (during polymerization) – see claim 2 of the patent and column 7, lines 11-12. A person of nominal skill in the art would not mistake this for the formation of microparticles in situ upon coming in contact with aqueous fluids.	The term "in situ" as used herein is intended to mean the formation of microcarriers when the gelled dispersion comes into contact with aqueous fluids either in the body or in an external environment.
7.	The composition upon coming in contact with an aqueous medium would stay intact and not fall apart into microparticles – with a resultant insignificant change in the specific surface area. The microdroplets or preformed microcarriers entrapped within the hydrogel matrix will not be	The composition upon coming in contact with an aqueous medium falls apart into microcarriers rapidly – (See examples 19-23, 26-38, and 40-51) with a resultant extremely significant increase in the specific surface area.

	released until the hydrogel has disintegrated completely. The hydrogel swells rapidly and does not fall apart rapidly as it is insoluble; see column 1, lines 21-25.	
8.	The composition would generally be presented as a dry product to be implanted or as dry microspheres where the viscosity of the product increases upon coming into contact with aqueous media through the swelling of the hydrogel.	The product would always be available as a gelled dispersion, ready-for-administration where the viscosity of the composition drops upon coming into contact with aqueous media.

The microdroplets described by Sawhney are different from those described in the instant application.

The droplet-in-oil dispersions described in Sawhney and those in the instant application are completely different as described in the table above. Sawhney has used the description of biodegradable polymers only to describe the prior art and the problems associated with such products and does not describe the use of such polymers in their composition. This is neither contemplated, described or claimed in the invention.

The use of solvents to form microspheres (col. 13, lines 51-60) is intended for the use of these solvents as phase transfer agents during polymerization of the continuous phase for the formation of the hydrogel matrix as these solvents have limited solubilities in the non-aqueous component of the composition and perhaps a higher solubility in the aqueous components of the composition. The solvents have not been described to be used for the dissolution of the biodegradable polymer for the formation of microcarriers.

Sawhney teaches the use of sorbitan monostearate as a release rate modifying agent (col. 14, lines 10-19 and col. 16, lines 59-60) to be added to the hydrophobic domains of the

composition. But, the patent does not describe the use of sorbitan monostearate to form a oily gelled continuous phase in which polymer solutions carrying biologically active agents can be dispersed and effectively stabilized to form microcarriers in situ upon coming in contact with aqueous media.

Col. 7, lines 11-12 talk about in situ formation of the microparticles. This pertains to the formation in situ of the microparticles during the polymerization of the hydrogel. This is clearly defined and cannot be confused as "the site of application in the body" unless the polymerization is to be carried out in the body, which is not the intention of the patent.

With regard to claim 2 : Sawhney includes polylactic acid and copolymers of lactic and glycolic acid (PLGA) among the polymers used to form biodegradable microspheres (col. 2, lines 50-61). The use of polymers is described as used in the prior art. The Sawhney patent does not describe the use of these polymers in the hydrogel matrix to form microcarriers in situ. Also, the instant application provides enough description and examples about the lacunae in the prior art delivery compositions using these polymers and also the use of the instant application in overcoming these lacunae.

Regarding claims 5, 54 and 55, Sawhney teaches that any pharmaceutically acceptable oil may be used, including peanut, castor, coconut and corn oil (col. 13, lines 37-39) : As explained above, the oil forms part of the internal hydrophobic domain in the Sawhney patent, whereas it forms the continuous phase in the instant application with a completely different purpose for its addition.

Regarding claim 6: The sorbitan monostearate is incapable of gelling the aqueous phase as it is insoluble in water. Also, small quantities of solvents present in the hydrogel matrix are used as phase transfer agents and not as polymer solvents as in the instant application. Further, the sorbitan monostearate is used in the Sawhney patent as a release rate controlling agent also in the hydrophobic domain.

With respect to claims 7, 8 and 63: The two delivery compositions are completely different. Thus, the same biologically active agents can be included in the applications.

With respect to claim 11 : The interpretation of the phrase "*in situ*" is described above as being completely different in both applications. Col. 7, lines 11-12 of Sawhney describe that it is the size of the microspheres that directs their placement. This does not describe the formation of microspheres *in situ*.

With respect to claims 12 and 13: The Sawhney patent does not use a polymer; rather a polymer is formed in situ by polymerization entrapping hydrophobic domains within.

With respect to claim 14: The microspheres of any shape and size used in the Sawhney patent pertain to the use of preformed microparticles which are added to the aqueous macromer solution which is further polymerized into a hydrogel. The instant application does not use preformed microparticles. Further, the microparticles used in the Sawhney application are non-polymeric.

With respect to claims 15-17: Since preformed particles are not added this is irrelevant to the instant application as the particles here are formed in situ in the body.

With respect to claims 52 and 63 : The two delivery compositions and the way they deliver drugs are different.

The standard test used to establish *prima facie* obviousness is the test set out by the Supreme Court in *Graham v. John Deere* (383 US 1, 148 USPQ 459 (1966)). To determine whether a claim is *prima facie* obvious:

1) the scope and content of the prior art are to be determined;

2) the differences between the prior art and the claims at issue are to be ascertained; and

3) the level of ordinary skill in the pertinent art resolved.

In addition, according to MPEP 2141, citing *Hodosh v. Block Drug Co., Inc.,* 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n. 5 (Fed. Cir. 1986), when applying 35 USC 103, the following tenets of patent law must be adhered to:

1) the claimed invention must be considered as a whole;

2) the references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination; and

3) the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention.

The reason, suggestion or motivation to combine references may be found explicitly or implicitly. While the references need not expressly teach that the disclosure contained therein should be combined with another, the showing of combinability must be clear and particular. *Ruiz v. A.B. Chance Co.,* 57 USPQ2d 1161 (Fed. Cir. 2000).

When the invention claimed in this application is considered as a whole; and Sawney is considered as a whole, there is no suggestion of the desirability and thus the obviousness of making the invention claimed in this application.

This comparative description shows that the compositions of Sawhney and those claimed in this application are different and that the compositions claimed in this application are not obvious in view of Sawhney.

Accordingly, claims 1, 2, 5-8, 11-17, 52, 54, 55, and 63 are not obvious in view of Sawhney and it is respectfully requested that this rejection be withdrawn.

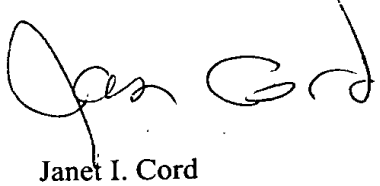
The Examiner has rejected claims 4 and 10 as being obvious over the combination of Sawhney and Borisy et al. (US patent 6,569,853). Applicants respectfully traverse this rejection.

As explained above the delivery compositions of Sawhney and this application are clearly different. Two delivery compositions which are principally different in composition and mechanism of delivery can deliver the same biologically active ingredient. The release profiles of any active agent are expected to be completely different when delivered by the two delivery compositions. Thus, though both delivery compositions talk about drug delivery, each composition would deliver the drug in a completely different fashion. It would not be obvious for a person with ordinary skill in the art to have a reasonable expectation that the two delivery compositions would release the active agent in a similar fashion.

Accordingly it is respectfully requested that this rejection be withdrawn.

Applicants submit that this application is in condition for allowance and favorable consideration is respectfully requested.

Respectfully submitted,



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Sorbitan Esters (Sorbitan Fatty Acid Esters)

1. Nonproprietary Names

BP: Sorbitan laurate
Sorbitan oleate
Sorbitan palmitate
Sorbitan stearate
Sorbitan trioleate

JP: Sorbitan sesquioleate

PhEur: Sorbitani lauras
Sorbitani oleas
Sorbitani palmitas
Sorbitani stearas
Sorbitani trioleati trioleas

USP: Sorbitan monolaurate (sorbitan, esters monodecanoate)
Sorbitan monooleate
Sorbitan monopalmitate
Sorbitan monostearate
Sorbitan sesquioleate
Sorbitan trioleate

2. Synonyms

See Table I.

3. Chemical Names and CAS Registry Numbers

See Table II.

Table I: Synonyms of selected sorbitan esters.

Name	Synonym
Sorbitan monoisostearate	1,4-Anhydro-D-glucitol, 6-isooctadecanoate; anhydrosorbitol monoisostearate; *Arlacel 987*; *Crill 6*; sorbitan isostearate.
Sorbitan monolaurate	493; *Arlacel 20*; *Armotan ML*; *Crill 1*; *Glycomul L*; *Hodag SML*; *Liposorb L*; *Montane 20*; *Protachem SML*; *Sorbester P12*; *Sorbirol L*; sorbitan laurate; *Span 20*.
Sorbitan monooleate	494; *Ablunol S-80*; *Arlacel 80*; *Armotan MO*; *Capmul O*; *Crill 4*; *Crill 50*; *Drewmulse SMO*; *Drewsorb 80K*; *Glycomul O*; *Hodag SMO*; *Lamesorb SMO*; *Liposorb O*; *Montane 80*; *Nikkol SO-10*; *Nissan Nonion OP-80R*; *Norfox Sorbo S-80*; *Polycon S80 K*; *Proto-sorb SMO*; *S-Maz 80K*; *Protachem SMO*; *Sorbester P17*; *Sorbirol O*; *Sorgen 40-*; *Sorgon S-40-H*; sorbitan oleate; *Span 80*.
Sorbitan monopalmitate	495; 1,4-Anhydro-D-glucitol, 6-hexadecanoate; *Ablunol S-40*; *Arlacel 40*; *Armotan MP*; *Crill 2*; *Glycomul P*; *Hodag SMP*; *Lamesorb SMP*; *Liposorb P*; *Montane 40*; *Nikkol SP-10*; *Nissan Nonion PP-40R*; *Protachem SMP*; *Proto-sorb SMP*; *Sorbester P16*; *Sorbirol P*; sorbitan palmitate; *Span 40*.
Sorbitan monostearate	491; *Ablunol S-60*; *Alkamuls SMS*; 1,4-Anhydro-D-glucitol, 6-octadecanoate; anhydrosorbitol monostearate; *Arlacel 60*; *Armotan MS*; *Atlas 110K*; *Capmul S*; *Crill 3*; *Drewmulse SMS*; *Drewsorb 60K*; *Durtan 60*; *Durtan 60K*; *Famodan MS Kosher*; *Glycomul S FG*; *Glycomul S KFG*; *Hodag SMS*; *Lamesorb SMS*; *Liposorb S*; *Liposorb SC*; *Liposorb S-K*; *Montane 60*; *Nissan Nonion SP-60R*; *Norfox Sorbo S-60FG*; *Polycon S60K*; *Prote-sorb SMS*; *Protachem SMS*; *S-Maz 60K*; *S-Maz 60KHS*; *Sorgen 50*; *Sorbester P18*; *Sorbirol S*; sorbitan stearate; *Span 60*; *Span 60K*; *Span 60 VS*.
Sorbitan sesqui-isostearate	*Protachem SQI*.
Sorbitan sesquioleate	*Arlacel C*; *Arlacel 83*; *Crill 43*; *Glycomul SOC*; *Hodag SSO*; *Liposorb SQO*; *Montane 83*; *Nikkol SO-15*; *Nissan Nonion OP-83RAT*; *Protachem SOC*; *Sorgen 30*; *Sorgen S-30-H*.
Sorbitan trilaurate	*Span 25*.
Sorbitan trioleate	*Ablunol S-85*; *Arlacel 85*; *Crill 45*; *Glycomul TO*; *Hodag STO*; *Liposorb TO*; *Montane 85*; *Nissan Nonion OP-85R*; *Prote-sorb STO*; *S-Maz 85K*; *Protachem STO*; *Sorbester P37*; *Span 85*.
Sorbitan tristearate	492; *Alkamuls STS*; *Crill 35*; *Crill 41*; *Drewsorb 65K*; *Famodan TS Kosher*; *Glycomul TS KFG*; *Hodag STS*; *Lamesorb STS*; *Liposorb TS*; *Liposorb TS-K*; *Montane 65*; *Protachem STS*; *Proteo-sorb STS*; *Sorbester P38*; *Span 65*; *Span 65K*.

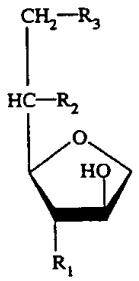
Table II: Chemical name and CAS Registry Number of selected sorbitan esters.

Name	Chemical name	CAS number
Sorbitan di-isostearate	Sorbitan di-isooctadecanoate	[68238-87-9]
Sorbitan dioleate	(Z,Z)-Sorbitan di-9-octadecanoate	[29116-98-1]
Sorbitan monolaurate	Sorbitan monododecanoate	[1338-39-2]
Sorbitan monoisostearate	Sorbitan monoisooctadecanoate	[71902-01-7]
Sorbitan monooleate	(Z)-Sorbitan mono-9-octadecenoate	[1338-43-8]
Sorbitan monopalmitate	Sorbitan monohexadecanoate	[26266-57-9]
Sorbitan monostearate	Sorbitan mono-octadecanoate	[1338-41-6]
Sorbitan sesqui-isostearate	Sorbitan sesqui-isooctadecanoate	[71812-38-9]
Sorbitan sesquioleate	(Z)-Sorbitan sesqui-9-octadecenoate	[8007-43-0]
Sorbitan sesquistearate	Sorbitan sesqui-octadecanoate	[51938-44-4]
Sorbitan tri-isostearate	Sorbitan tri-isooctadecanoate	[54392-27-7]
Sorbitan trioleate	(Z,Z,Z)-Sorbitan tri-9-octadecenoate	[26266-58-0]
Sorbitan tristearate	Sorbitan tri-octadecanoate	[26658-19-5]

4. Empirical Formula Molecular Weight

Name	Formula	Molecular weight
Sorbitan di-isostearate	$C_{42}H_{80}O_7$	697
Sorbitan dioleate	$C_{42}H_{76}O_7$	693
Sorbitan monoisostearate	$C_{24}H_{46}O_6$	431
Sorbitan monolaurate	$C_{18}H_{34}O_6$	346
Sorbitan monooleate	$C_{24}H_{44}O_6$	429
Sorbitan monopalmitate	$C_{22}H_{42}O_6$	403
Sorbitan monostearate	$C_{24}H_{46}O_6$	431
Sorbitan sesqui-isostearate	$C_{33}H_{63}O_{6.5}$	564
Sorbitan sesquioleate	$C_{33}H_{60}O_{6.5}$	561
Sorbitan sesquistearate	$C_{33}H_{63}O_{6.5}$	564
Sorbitan tri-isostearate	$C_{60}H_{114}O_8$	964
Sorbitan trioleate	$C_{60}H_{108}O_8$	958
Sorbitan tristearate	$C_{60}H_{114}O_8$	964

5. Structural Formula



$R_1 = R_2 = OH$, $R_3 = R$ for sorbitan monoesters,
$R_1 = OH$, $R_2 = R_3 = R$ for sorbitan diesters,
$R_1 = R_2 = R_3 = R$ for sorbitan triesters,

Where R = $(C_{17}H_{35})COO$ for isostearate,
$(C_{11}H_{23})COO$ for laurate,
$(C_{17}H_{33})COO$ for oleate,
$(C_{15}H_{31})COO$ for palmitate,
$(C_{17}H_{35})COO$ for stearate.

The sesqui-esters are equimolar mixtures of monoesters and diesters.

6. Functional Category

Emulsifying agent; nonionic surfactant; solubilizing agent; wetting and dispersing/suspending agent.

7. Applications in Pharmaceutical Formulation or Technology

Sorbitan monoesters are a series of mixtures of partial esters of sorbitol and its mono- and di-anhydrides with fatty acids. Sorbitan diesters are a series of mixtures of partial esters of sorbitol and its mono-anhydride and with fatty acids.

Sorbitan esters are widely used in cosmetics, food products, and pharmaceutical formulations as lipophilic nonionic surfactants. They are mainly used in pharmaceutical formulations as emulsifying agents in the preparation of creams, emulsions, and ointments for topical application. When used alone, sorbitan esters produce stable water-in-oil emulsions and microemulsions but are frequently used in combination with varying proportions of a polysorbate to produce water-in-oil or oil-in-water emulsions or creams of varying consistencies.

Sorbitan monolaurate, sorbitan monopalmitate and sorbitan trioleate have also been used at a concentration of 0.01-0.05% w/v in the preparation of an emulsion for intramuscular administration.

Use	Concentration (%)
Emulsifying agent	
Used alone in water-in-oil emulsions	1-15
Used in combination with hydrophilic emulsifiers in oil-in-water emulsions	1-10
Used to increase the water-holding properties of ointments	1-10
Solubilizing agent	
For poorly soluble, active constituents in lipophilic bases	1-10
Wetting agent	
For insoluble, active constituents in lipophilic bases	0.1-3

8. Description

Sorbitan esters occur as cream to amber-colored liquids or solids with a distinctive odor and taste, *see* below.

Name	Appearance
Sorbitan monoisostearate	Yellow viscous liquid
Sorbitan monolaurate	Yellow viscous liquid
Sorbitan monooleate	Yellow viscous liquid
Sorbitan monopalmitate	Cream solid
Sorbitan monostearate	Cream solid
Sorbitan sesquioleate	Amber viscous liquid
Sorbitan trioleate	Amber viscous liquid
Sorbitan tristearate	Cream/yellow solid

9. Pharmacopeial Specifications

Test	JP	PhEur	USP
Identification	+	+	+
Acid value			
Sorbitan monolaurate	—	≤ 7.0	≤ 8
Sorbitan monooleate	—	≤ 8.0	≤ 8
Sorbitan monopalmitate	—	≤ 8.0	≤ 8
Sorbitan monostearate	—	≤ 10.0	≤ 10
Sorbitan sesquioleate	—	—	≤ 14
Sorbitan trioleate	—	≤ 16.0	≤ 17
Hydroxyl value			
Sorbitan monolaurate	—	330-358	330-358
Sorbitan monooleate	—	193-210	190-215
Sorbitan monopalmitate	—	270-305	275-305
Sorbitan monostearate	—	235-260	235-260
Sorbitan sesquioleate	—	—	182-220
Sorbitan trioleate	—	55-75	50-75
Iodine value			
Sobitan monolaurate	—	≤ 10.0	—
Sorbitan monooleate	—	62-76	62-76
Sorbitan sesquioleate	—	—	65-75
Sorbitan trioleate	—	76-90	77-85
Peroxide value			
Sorbitan monolaurate	—	≤ 5.0	—
Sorbitan monooleate	—	≤ 10.0	—
Sorbitan monopalmitate	—	≤ 5.0	—
Sorbitan monostearate	—	≤ 5.0	—
Sorbitan trioleate	—	≤ 10.0	—

(Continued)

Test	JP	PhEur	USP
Saponification value			
Sorbitan monolaurate	—	158-170	158-170
Sorbitan monooleate	—	149-160	145-160
Sorbitan monopalmitate	—	140-155	140-150
Sorbitan monostearate	—	147-157	147-157
Sorbitan sesquioleate	150-168	—	143-165
Sorbitan trioleate	—	170-190	169-183
Water			
Sorbitan monolaurate	—	≤ 1.5%	≤ 1.5%
Sorbitan monooleate	—	≤ 1.5%	≤ 1.0%
Sorbitan monopalmitate	—	≤ 1.5%	≤ 1.5%
Sorbitan monostearate	—	≤ 1.5%	≤ 1.5%
Sorbitan sesquioleate	≤ 3.0	—	≤ 1.0%
Sorbitan trioleate	—	≤ 1.5%	≤ 0.7%
Residue on ignition			
Sorbitan monolaurate	—	—	≤ 0.5%
Sorbitan monooleate	—	—	≤ 0.5%
Sorbitan monopalmitate	—	—	≤ 0.5%
Sorbitan monostearate	—	—	≤ 0.5%
Sorbitan sesquioleate	≤ 1.0%	—	≤ 1.4%
Sorbitan trioleate	—	—	≤ 0.25%
Sulfated ash	—	—	—
Total ash	—	≤ 0.5%	—
Heavy metals	≤ 20 ppm	—	≤ 0.001%
Arsenic	≤ 2 ppm	—	—
Specific gravity			
Sorbitan sesquioleate	0.960-1.020	—	—
Assay for fatty acids			
Sorbitan monolaurate	—	—	55.0-63.0%
Sorbitan monooleate	—	—	72.0-78.0%
Sorbitan monopalmitate	—	—	63.0-71.0%
Sorbitan monostearate	—	—	68.0-76.0%
Sorbitan sesquioleate	—	—	74.0-80.0%
Sorbitan trioleate	—	—	85.5-90.0%
Assay for polyols			
Sorbitan monolaurate	—	—	39.0-45.0%
Sorbitan monooleate	—	—	25.0-31.0%
Sorbitan monopalmitate	—	—	32.0-38.0%
Sorbitan monostearate	—	—	27.0-34.0%
Sorbitan sesquioleate	—	—	22.0-28.0%
Sorbitan trioleate	—	—	13.0-19.0%

10. Typical Properties

Acid value: *see* Table III
Density: *see* Table III
Flash point: > 149°C
HLB value: *see* Table III
Hydroxyl value: *see* Table III
Iodine number: *see* Table III
Melting point: *see* Table III
Moisture content: *see* Table IV
Pour point: *see* Table III
Saponification value: *see* Table IV
Solubility: sorbitan esters are generally soluble or dispersible in oils; they are also soluble in most organic solvents. In water, although insoluble they are generally dispersible.
Surface tension: *see* Table IV
Viscosity (dynamic): *see* Table IV

11. Stability and Storage Conditions

Gradual soap formation occurs with strong acids or bases; sorbitan esters are stable in weak acids or bases.

Sorbitan esters should be stored in a well-closed container in a cool, dry, place.

12. Incompatibilities

–

13. Method of Manufacture

Sorbitol is dehydrated to form a hexitan (1,4-sorbitan) which is then esterified with the desired fatty acid.

14. Safety

Sorbitan esters are widely used in cosmetics, food products, and oral and topical pharmaceutical formulations and are generally regarded as nontoxic and nonirritant materials. However, there have been occasional reports of hypersensitive skin reactions following the topical application of products containing sorbitan esters.[1-4] When heated to decomposition the sorbitan esters emit acrid smoke and irritating fumes.

The WHO has set an estimated acceptable daily intake of sorbitan monopalmitate, monostearate and tristearate,[5] and sorbitan monolaurate, and monooleate[6] at up to 25 mg/kg body-weight calculated as total sorbitan esters.

Sorbitan monolaurate: LD_{50} (rat, oral): 33.6 g/kg.[7] Experimental neoplastigen.

Sorbitan monostearate: LD_{50} (rat, oral): 31 g/kg.[7] Very mildly toxic by ingestion. Experimental reproductive effects.

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended.

16. Regulatory Status

Certain sorbitan esters are accepted as food additives in the UK. Sorbitan esters are included in the FDA Inactive Ingredients Guide (inhalations, IM injections, ophthalmic, oral, topical, and vaginal preparations). Sorbitan esters are used in nonparenteral medicines licensed in the UK.

17. Pharmacopeias

Name	Pharmacopeia
Sorbitan monolaurate	Eur and US
Sorbitan monooleate	Eur and US
Sorbitan monopalmitate	Eur and US
Sorbitan monostearate	Eur and US
Sorbitan sesquioleate	Jpn, Swiss, and US
Sorbitan trioleate	Eur and US

18. Related Substances

Polyoxyethylene sorbitan fatty acid esters.

Table III: Typical properties of selected sorbitan esters.

Name	Acid value	Density (g/cm^3)	HLB value	Hydroxyl value	Iodine number	Melting point (°C)	Pour point (°C)
Sorbitan monoisostearate	≤ 8	—	4.7	220-250	—	—	—
Sorbitan monolaurate	≤ 7	1.01	8.6	159-169	≤ 7	—	16-20
Sorbitan monooleate	≤ 8	1.01	4.3	193-209	—	—	-12
Sorbitan monopalmitate	3-7	1.0	6.7	270-303	≤ 1	43-48	—
Sorbitan monostearate	5-10	—	4.7	235-260	≤ 1	53-57	—
Sorbitan sesquioleate	8.5-13	1.0	3.7	188-210	—	—	—
Sorbitan trioleate	10-14	0.95	1.8	55-70	—	—	—
Sorbitan tristearate	≤ 7	—	2.1	60-80	—	—	—

Table IV: Typical properties of selected sorbitan esters.

Name	Saponification value	Surface tension of 1% aqueous solution (mN/m)	Viscosity at 25°C (mPa s)	Water content (%)
Sorbitan monoisostearate	143-153	—	—	≤ 1.0
Sorbitan monolaurate	159-169	28	3900-4900	≤ 0.5
Sorbitan monooleate	149-160	30	970-1080	≤ 0.5
Sorbitan monopalmitate	142-152	36	Solid	≤ 1.0
Sorbitan monostearate	147-157	46	Solid	≤ 1.0
Sorbitan sesquioleate	149-160	—	1500	≤ 1.0
Sorbitan trioleate	170-190	32	200-250	≤ 1.0
Sorbitan tristearate	172-185	48	Solid	≤ 1.0

19. Comments

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20. Specific References

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22. Authors

MJ Lawrence.

Sorbitan Stearate

(5)

General Notices

1338-41-6

Sorbitan Stearate complies with the requirements of the 4th edition of the European Pharmacopoeia [1043]. These requirements are reproduced after the heading `Definition' below.

Action and use Pharmaceutical aid.
When sorbitan monostearate is demanded, Sorbitan Stearate shall be supplied.

Ph Eur

DEFINITION

Mixture usually obtained by partial esterification of sorbitol and its mono- and di-anhydrides with *Stearic acid 50 (1474)* or *Stearic acid 70 (1474)*.

CHARACTERS

Appearance: pale yellow, waxy solid.

Solubility: practically insoluble, but dispersible in water, slightly soluble in alcohol. pl. refer

IDENTIFICATION

A. Melting point (*2.2.15*): 50°C to 60°C.

Introduce the melted substance into the capillary tubes and allow to stand at a temperature below 10°C for 24 h.

B. It complies with the test for hydroxyl value (see Tests).

C. It complies with the test for composition of fatty acids (see Tests).

TESTS

Acid value (*2.5.1*): maximum 10.0, determined on 5.0 g.

Hydroxyl value (*2.5.3, Method A*): 235 to 260.

Peroxide value (*2.5.5*): maximum 5.0.

Saponification value (*2.5.6*): 147 to 157.

Carry out the saponification for 1 h.

Composition of fatty acids. Gas chromatography (*2.4.22, Method C*).

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Composition of the fatty acid fraction of the subtance:

	Type of fatty acid used	Composition of fatty acids
Sorbitan stearate (type I)	Stearic acid 50	*Stearic acid*: 40.0 per cent to 60.0 per cent, *Sum of the contents of palmitic and stearic acids*: minimum 90.0 per cent.
Sorbitan stearate (type II)	Stearic acid 70	*Stearic acid*: 60.0 per cent to 80.0 per cent, *Sum of the contents of palmitic and stearic acids*: minimum 90.0 per cent.

Heavy metals (*2.4.8*): maximum 10 ppm.

2.0 g complies with limit test D. Prepare the standard using 2 ml of *lead standard solution (10 ppm Pb) R*.

Water (*2.5.12*): maximum 1.5 per cent, determined on 1.00 g.

Total ash (*2.4.16*): maximum 0.5 per cent.

STORAGE

Protected from light.

LABELLING

The label states the type of sorbitan stearate.

Ph Eur

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Sorbitan Palmitate

General Notices

26266-57-9

Sorbitan Palmitate complies with the requirements of the 4th edition of the European Pharmacopoeia [1042]. These requirements are reproduced after the heading `Definition' below.

Action and use Pharmaceutical aid.
When sorbitan monopalmitate is demanded, Sorbitan Palmitate shall be supplied.

Ph Eur

DEFINITION

Mixture usually obtained by partial esterification of sorbitol and its mono- and di-anhydrides with palmitic acid.

CHARACTERS

Appearance: yellow or yellowish powder, waxy flakes or hard masses.

Solubility: practically insoluble in water, soluble in fatty oils, slightly soluble in alcohol.

Pl. refer

IDENTIFICATION

A. Melting point (*2.2.15*): 44°C to 51°C.

Introduce the melted substance into the glass capillary tubes and allow to stand at a temperature below 10°C for 24 h.

B. It complies with the test for hydroxyl value (see Tests).

C. It complies with the test for composition of fatty acids (see Tests).

TESTS

Acid value (*2.5.1*): maximum 8.0, determined on 5.0 g.

Hydroxyl value (*2.5.3, Method A*): 270 to 305.

Peroxide value (*2.5.5*): maximum 5.0.

Saponification value (*2.5.6*): 140 to 155.

Carry out the saponification for 1 h.

Composition of fatty acids. Gas chromatography (*2.4.22, Method C*).

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(8)

Composition of the fatty acid fraction of the substance:
— *palmitic acid:* minimum 92.0 per cent,
— *stearic acid:* maximum 6.0 per cent.

Heavy metals (*2.4.8*): maximum 10 ppm.

2.0 g complies with limit test D. Prepare the standard using 2 ml of *lead standard solution (10 ppm Pb) R*.

Water (*2.5.12*): maximum 1.5 per cent, determined on 1.00 g.

Total ash (*2.4.16*): maximum 0.5 per cent.

STORAGE

Protected from light.

Ph Eur

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Saponification value (*2.5.6*): 158 to 170.

Carry out the saponification for 1 h.

Composition of fatty acids. Gas chromatography (*2.4.22, Method C*).

Prepare reference solution (a) as indicated in tables 2.4.22.-1 and 2.4.22.-2.

Composition of the fatty acid fraction of the substance:

- *caproic acid*: maximum 1.0 per cent,
- *caprylic acid*: maximum 10.0 per cent,
- *capric acid*: maximum 10.0 per cent,
- *lauric acid*: 40.0 per cent to 60.0 per cent,
- *myristic acid*: 14.0 per cent to 25.0 per cent,
- *palmitic acid*: 7.0 per cent to 15.0 per cent,
- *stearic acid*: maximum 7.0 per cent,
- *oleic acid*: maximum 11.0 per cent,
- *linoleic acid*: maximum 3.0 per cent.

Heavy metals (*2.4.8*): maximum 10 ppm.

2.0 g complies with limit test D. Prepare the standard using 2 ml of *lead standard solution (10 ppm Pb) R.*

Water (*2.5.12*): maximum 1.5 per cent, determined on 1.00 g.

Total ash (*2.4.16*): maximum 0.5 per cent.

STORAGE

Protected from light.

01/2002:1041

SORBITAN OLEATE

Sorbitani oleas

DEFINITION

Mixture usually obtained by partial esterification of sorbitol and its mono- and di-anhydrides with oleic acid.

CHARACTERS

Appearance: brownish-yellow, viscous liquid.

Solubility: practically insoluble, but dispersible in water, soluble in fatty oils producing a hazy solution, miscible with alcohol.

Relative density: about 0.99.

IDENTIFICATION

A. It complies with the test for hydroxyl value (see Tests).

B. It complies with the test for iodine value (see Tests).

C. It complies with the test for composition of fatty acids (see Tests).

TESTS

Acid value (*2.5.1*): maximum 8.0, determined on 5.0 g.

Hydroxyl value (*2.5.3, Method A*): 190 to 210, determined on 2.0 g.

Iodine value (*2.5.4*): 62 to 76.

Peroxide value (*2.5.5*): maximum 10.0.

Saponification value (*2.5.6*): 145 to 160.

Carry out the saponification for 1 h.

Composition of fatty acids. Gas chromatography (*2.4.22, Method C*).

Composition of the fatty acid fraction of the substance:

- *myristic acid*: maximum 5.0 per cent,
- *palmitic acid*: maximum 16.0 per cent,
- *palmitoleic acid*: maximum 8,0 per cent,
- *stearic acid*: maximum 6.0 per cent,
- *oleic acid*: 65.0 per cent to 88.0 per cent,
- *linoleic acid*: maximum 18.0 per cent,
- *linolenic acid*: maximum 4.0 per cent,
- *fatty acids with chain length greater than* C_{18}: maximum 4.0 per cent.

Heavy metals (*2.4.8*): maximum 10 ppm.

2.0 g complies with limit test D. Prepare the standard using 2 ml of *lead standard solution (10 ppm Pb) R.*

Water (*2.5.12*): maximum 1.5 per cent, determined on 1.00 g.

Total ash (*2.4.16*): maximum 0.5 per cent.

STORAGE

Protected from light.

01/2002:1042

SORBITAN PALMITATE

Sorbitani palmitas

DEFINITION

Mixture usually obtained by partial esterification of sorbitol and its mono- and di-anhydrides with palmitic acid.

CHARACTERS

Appearance: yellow or yellowish powder, waxy flakes or hard masses.

Solubility: practically insoluble in water, soluble in fatty oils, slightly soluble in alcohol.

IDENTIFICATION

A. Melting point (*2.2.15*): 44 °C to 51 °C.
Introduce the melted substance into the glass capillary tubes and allow to stand at a temperature below 10 °C for 24 h.

B. It complies with the test for hydroxyl value (see Tests).

C. It complies with the test for composition of fatty acids (see Tests).

TESTS

Acid value (*2.5.1*): maximum 8.0, determined on 5.0 g.

Hydroxyl value (*2.5.3, Method A*): 270 to 305.

Peroxide value (*2.5.5*): maximum 5.0.

Saponification value (*2.5.6*): 140 to 155.

Carry out the saponification for 1 h.

Composition of fatty acids. Gas chromatography (*2.4.22, Method C*).

Composition of the fatty acid fraction of the substance:

- *palmitic acid*: minimum 92.0 per cent,
- *stearic acid*: maximum 6.0 per cent.

Heavy metals (*2.4.8*): maximum 10 ppm.

2.0 g complies with limit test D. Prepare the standard using 2 ml of *lead standard solution (10 ppm Pb) R.*

Water (*2.5.12*): maximum 1.5 per cent, determined on 1.00 g.

Total ash (*2.4.16*): maximum 0.5 per cent.

STORAGE

Protected from light.